

Remarks

Claims 1 and 3-69 were pending. Claims 13-14, 33-34, and 53-54 have been cancelled without prejudice and 1, 7, 9, 27-29, 47-49, and 67-69 have been amended above. Upon entry of the present Amendment, claims 1, 3-12, 15-32, 35-52, and 55-69 will be pending and in condition for allowance.

The claims have been amended, *inter alia*, in order to incorporate a preferred concentration range into each of the independent claims, and thereby facilitate the prosecution of the present application. As discussed both previously and below, the combination of elements presently claimed is neither taught or suggested by the cited art. The cancelled claims are considered patentable for these and other reasons as well, and will likely be considered in the course of one or more continuing cases.

The rejection under Section 103(a) based on Mundshenk et al. with Heiber et al. and Siegel et al. is respectfully traversed. Mundschenk '407 is cited for its teaching of the preparation of inactivated bioactive peptides, while Heiber et al. is cited as teaching "buccally administered peptides", and Siegel et al. is cited, essentially, for its inclusion of benzalkonium chloride in a delivery composition (though described as a "preservative"). None of these disparate references, however, either alone or in suitable combination, teach or suggest the use of a quaternary ammonium salt (such as benzalkonium chloride) to *itself* provide effective permeation of an *inactivated bioactive peptide* into a mucosal surface, and particularly into a mucosal surface of the mouth.

Mundschenk et al. (WO 97/43407) merely represents Applicant's own prior teaching of the preparation and use of preferred inactivated bioactive peptides. Stated simply, there is nothing in the reference itself that teaches or suggests buccal delivery in this manner, let alone using the formulation presently described and claimed. Delivery routes and related systems can vary widely, and there is little or no certainty that the ability to deliver a protein via one route, is suggestive or predictive of its delivery via another. Nor, in turn, does the ability of a system to deliver one type of protein necessarily suggest or predict its ability to deliver another.

Nor has the Examiner yet cited any reference that suggests the delivery of an "inactivated bioactive peptide" in the buccal cavity, using any system or approach whatsoever. In fact, Heiber et al. 5,766,620 has merely been cited for the proposition that "peptides are buccally administratable". The Action continues to ignore the fact, however, that Heiber et al. do not describe the peptides of the present invention, nor do the compositions of Heiber et al. include the use of benzalkonium chloride, particularly in the manner presently claimed.

Nor do Siegel et al. remedy the defects of the previous two references, including those described above. Siegel et al. merely investigate the effect of various surfactants, including benzalkonium chloride, on the permeability of canine mucosa, using a variety of test molecules. At its *closest*, the reference evaluates the effect of benzalkonium chloride (at concentrations of 0.025%, 0.1% and 1.0%) on the permeability of insulin. Note that only the *lowest* of these concentrations is even within the enhancer concentration range now claimed. The data at Table I

of Siegel et al., however, shows that this lowest concentration fails to provide *any* significant improvement as compared to the control. It is only at significantly higher concentrations (and now well exceeding Applicant's currently claimed range) that "permeability" is increased. Rather than true permeability, however, the increase at these concentrations would presumably be due, in large part, to the severe disruptive effect the surfactant would be expected to have on membranes.

The rejection under Section 103(a) at Paragraph 8 of the Action is respectfully traversed. It would appear that the summary statement of the rejection is incorrect, and should instead refer to the combination of Mundshenk et al. with Kamiya et al. and Dondeti et al. (as opposed to Siegel et al.). Mundshenk et al., is distinguished for the reasons set forth above, and for others as well. Kamiya et al. is merely included as teaching the use of spraying to administer peptides. Putting aside its own deficiencies, this reference adds nothing to remedy the various shortcomings described above with respect to Mundshenk et al., or below with respect to Dondeti et al.

At its closest, Dondeti et al. merely describes the use of benzalkonium chloride as a *preservative*, and then only *in addition to* the use of 2-phenylethanol as an additional preservative. The effect of both preservatives, in turn, was evaluated *not* to determine their effect (collectively) on delivery, *per se*, but instead in view of the possible effects of such preservatives on "globule size" and on "ciliary beat frequency". These effects, however, are clearly unique to the "microcrystalline cellulose" composition of Dondeti et al., as compared to the present formulation, and to nasal, as compared to buccal, delivery. The Action appears to have no particular response to these positions regarding Dondeti et al.

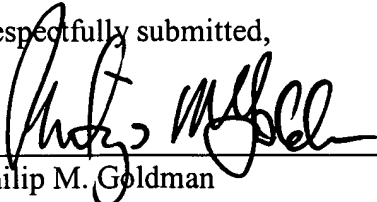
Finally, the rejection under Section 103(a) based on Mundshenk et al., Kamiya et al. and Cardinaux et al. is respectfully traversed. Mundshenk et al. and Kamiya et al. are distinguished for the reasons provided above. At its closest, Cardinaux et al. discloses mucosal peptide formulations with benzalkonium chloride as a mere preservative, and without apparent distinction over any of the other common preservatives described. Recognizing this, the Action states merely that the different and unexpected "use" of the present formulation is to be given no "patentable weight". It is both proper and necessary, however, to define the present system of claim 7 and formulation of claim 9 in terms of *both* the components of the formulation, and the manner in which they function.

Accordingly, entry of the present Amendment and reconsideration of the pending rejection is respectfully requested. The Examiner is encouraged to telephone the undersigned in the event any remaining issues arise.

The Commissioner is hereby authorized to charge any additional filing fees required to Deposit Account No. 061910. A duplicate copy of this sheet is enclosed.

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Respectfully submitted,



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